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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,289	07/13/2001	David Ian Rosnick	5051.518	3878

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EXAMINER
ALLEN, MARIANNE P

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,289	ROSNICK ET AL.	
	Examin r	Art Unit	
	Marianne P. Allen	1631	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *23-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-37* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-22, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 23-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claim Objections

Claim 17 is objected to because of the following informalities: A typographical error, "succssively". Appropriate correction is required.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See at least page 9 of the specification.

Claim Rejections - 35 USC § 112

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

Claims 1-20 are directed to a computer-based method for screening a nucleic acid sequence for efficient translation in a predetermined host. Claim 21 is directed to a system therefor. Claim 22 is directed to a computer program product therefor.

Claims 1, 21, and 22 recite that binding strengths between the ribosomal sequence and substrate nucleic acid sequence are determined at every alignment. A binding strength pattern is generated. The presence or absence of a three-base binding strength periodic cycle and phase through the substrate nucleic acid sequence is determined.

Claim 6 adds the limitation of determining the strength of the periodic signal.

Claim 7 adds the limitation of determining a quantitative indicator from the strength of the periodic signal.

Claims 8 and 9 add the limitation of replacing at least one base in the absence of sufficient translation efficiency.

Claims 8-10 add the limitation of determining sufficiency of translation efficiency.

Claim 11 adds the limitation of determining the phase shift in the three base periodic cycle.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

While the example (beginning at page 19) discloses a method of calculating free energy between base pairs and successively repeating the process for other alignments, the specification does not provide any examples or guidance for practicing the total method as claimed and by extension the computer program product and system therefor. In addition, the claims are not limited to this particular method of determining binding strength and the specification does not provide guidance to other methods of determining binding strength that could be used in the method as claimed. There is no guidance in the specification for generating a binding strength pattern and how to detect a three-base binding strength periodic cycle and phase from it. That is, the specification does not exemplify nor provide guidance on the conclusions to be drawn from any particular collection of binding energies. When is the pattern periodic enough to indicate the nucleic acid sequence is a candidate for efficient translation in the host? When is the phase correct enough to indicate the nucleic acid sequence is a candidate for efficient translation in the host? Within the context of the claims, what information does strength of the periodic signal (claim 6) provide with respect to efficient translation? What is the quantitative indicator required by claims 7-10? How is it computed from the strength of the periodic signal? The specification does not exemplify nor provide guidance on the replacement of at least one base in the substrate nucleic acid sequence to result in sufficiency of translation efficiency. Which position(s) should be replaced? What bases are to be used for replacement? What defines a nucleic acid sequence having sufficiency of translation? How is this attribute determined? (See claims 8-10.) With respect to claim 11, the specification does not exemplify nor provide guidance on detecting a phase shift and making an evaluation as to whether the substrate nucleic acid sequence remains a

candidate for efficient translation. Must some value be calculated? What defines a nucleic acid sequence having such a phase shift? How is this attribute determined?

It is further noted that Figures 5 and 6 are black box flow diagrams and include actions that are not limitations of the claims and that the specification provides no computer code to execute the method.

The invention as claimed would require undue experimentation to practice given the breadth of the claims in view of the lack of specific limitations as to how various values are to be determined, used, or evaluated; the prior art's apparent inability to perform such screenings for efficient translation; the need for experimentation to find a way to implement an operable method encompassed by the claims; the limited direction or guidance presented; the absence of working examples; and the complexity of bioinformatics even in view of the high level of skill of those in the art.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step (f) requires successively repeating steps (c) through (e) to determine a series of binding strengths. Step (g) is confusing in referring again to successively repeating steps (c) through (e). It appears that the binding strengths of the first, second, and third binding strengths and those of step (f) (i.e. each binding strength determined at every alignment) are used to generate the binding strength pattern. However, the language in step (g) implies that perhaps only the binding strengths determined in step (f) are used and that the first, second, and third

binding strengths are omitted. In addition, the claim does not make clear what type of "periodic cycle and phase" must be present to indicate that the substrate nucleic acid sequence is a candidate for efficient translation. The claim does not make clear what the metes and bounds of "correct phase" are. See also claims 21-22.

Claim 3 is confusing in reciting that the substrate sequence is obtained from a different host than the ribosomal nucleic acid sequence. Claim 2 upon which it depends already requires that the substrate nucleic acid is heterologous to the host and claim 1 upon which claim 2 depends requires that the ribosomal nucleic acid sequence be from the host. As such, the limitation of claim 3 appears to be implicit in claim 2, and thus claim 3 does not appear to further limit the subject matter of claim 2.

Claim 5 is confusing in reciting that the substrate nucleic acid sequence encodes a predetermined protein or peptide. Unless the substrate nucleic acid is one or two bases in length or is composed of a consecutive string of stop codons, all nucleic acids will encode a predetermined protein or peptide. That is, an open reading frame (or more than one open reading frame) that can be translated will be present. It is unclear if the recitation of "predetermined" was intended to imply some other feature of the substrate nucleic acid sequence.

Claim 8 is confusing in its dependency on claim 6. It appears it may have been intended to be dependent upon claim 7 as claim 6 has no step (i) or antecedent basis for the recited "quantitative indicator."

Claim 8 is further unclear as to whether the at least one base replacement is performed once (steps (c) through (j)) or successive times until the presence of sufficient translation efficiency is found. In view of dependent claim 10, the claim's intent appears to be that it would

occur once. It is unclear whether changes to the underlying encoded protein are permitted and/or what replacements can be made. It is unclear from the claim what level of translation efficiency is required to lead to the execution of step (k). Claim 9 is confusing for these same reasons.

Claim 9 is confusing in its dependency on claim 1. Claim 1 has no step (i) or antecedent basis for the recited "quantitative indicator."

Claim 10 does not make clear what level of efficiency of translation is required to meet the limitation of the claim and terminate the repeating steps.

Claim 14 is confusing in its dependency upon claim 1. The added final step is "predicting the potential for proper translation." This appears to be directed to a different method than claim 1 which is screening a nucleic acid sequence for efficient translation. That is, this final step does not result in the stated goal of claim 1. In addition, what is considered to be "proper"? Is this when the host actually translates it consistently with the prediction? "Potential" appears to imply some statistical likelihood; however, the claim is unclear.

Claim 15, part (i), recites that the binding strength pattern may be calculated by calculating a summation of all binding strengths. It is unclear how a single summation can be considered a binding pattern. Likewise, it is unclear how a single integral of all binding strengths (part (iii)) is a binding pattern and other calculations that lead to a single value. See also claim 16.

Claim 15 recites "selected from the group comprising..." This is not proper Markush language and the intended scope of the claim is unclear. See also claim 16.

Claims 18-20 are confusing in each reciting an additional step of calculating a value but failing to indicate that this information is used in any way to screen the nucleic acid sequence for efficient translation.

Claim 21 is directed to a system. The system comprises a variety of "means." It is unclear whether these "means" are intended to encompass hardware or software or some of both. If it is only intended to be computer usable storage medium having computer readable program code, then it does not appear to differ from the subject matter of claim 22. The term "system" is not considered to provide a specific limitation to a computer, monitor, keyboard, printer, and so forth.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Frishman et al. discloses an algorithm for finding ribosomal binding sites (RBS) and the correlation between the RBS properties and the potential gene start prediction accuracy. The reference does not disclose a method of screening for efficient translation in a predetermined host by determining a three-base binding strength periodic cycle and phase.

Hayes et al. discloses deriving ribosomal binding site (RBS) statistical models from unannotated DNA sequences and the use of the RBS model for N-terminal prediction. 16S rRNA sequences are used. The reference does not disclose a method of screening for efficient translation in a predetermined host by determining a three-base binding strength periodic cycle and phase.

Schurr et al. discloses identification and characterization of *E. coli* ribosomal binding sites by free energy computation. The free energies for all possible duplexes between the 16S rRNA 3' end and a region of 21 nucleotides upstream from the start codon were calculated. The reference notes that stabilitlity of the duplex between the rRNA and the Shine-Dalgarno region is not a distinctive measure between highly and poorly expressed genes. (See page 4022, right column.) The reference does not disclose a method of screening for efficient translation in a predetermined host by determining a three-base binding strength periodic cycle and phase.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 703-308-0666. The examiner can normally be reached on Monday-Friday, 8:30 am - 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703-308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Marianne P. Allen
Primary Examiner
Art Unit 1631

mpa
June 3, 2003